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(57) Abstract

New compositions adapted for nasal administration of medicaments are described.

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COMPOSITIONS FOR NASAL ADMINISTRATION

The present invention relates to a novel composition for nasal administration of medicaments.

The nasal passages may be used as a route of administration, for instance an ointment such as Bactroban Nasal may be applied to the anterior nares of the nose for a local topical effect. Spray formulations may applied to the nostrils. In addition, medicaments may administered to the lungs via the nostrils, using an aerosol or nebuliser. The nasal passages comprise mucosal tissues which might be used as means of systemically delivering a medicament. Such local topical or systemic delivery would be enhanced if the formulation was to have a prolonged residence time in the nasal passages.

Accordingly, the present invention provides a sprayable composition adapted for prolonged residence in the nasal passage, in particular the nasal pharynx, which comprises:

(a) an amphiphilic agent that increases in viscosity on contact with water;
(b) a non-aqueous diluent for the ampiphilic agent,
(c) a powdered medicament in suspension.

Amphiphilic agents are substances containing both hydrophilic and lipophilic groups. In liquid form, these agents are generally capable of spontaneous self-association in the presence of water, with a consequent increase in viscosity. This self-association results in a change in properties ranging from the formation of viscous liquids to semi-rigid gels. This behaviour has been characterised as due to the formation of long range order in the liquid system giving several distinct phases which have been called "liquid crystalline phases".

Materials known to exhibit such properties and which are suitable for use in a medicament formulation include mono-glycerides such as mono-olein and mono-linolein, phospholipids such as phosphatidyl cholines, and galactolipids such as galactoyl-diglycerides.

Typically the monoglycerides are long-chain fatty acid monoglycerides, optionally comprising up to 10% (w/w) of a long-chain fatty acid diglyceride and/or a small amount by weight of a free long-chain fatty acid. The mono- and di-glycerides may each include blends of different long-chain fatty acid mono- and di-glycerides. Suitable long-chain fatty acid monoglycerides include glycerol monooleate, glycerol monopalmitate and

glycerol monostearate. Suitable commercially available examples of such include the products available under the trade names MYVEROL, such as MYVEROL 18-99, MYVATEX, MYVAPLEX, and GMORPHIC 80 respectively, from Eastman Kodak Chemicals, Rochester, New York. A further useful long-chain fatty acid monoglyceride-containing product is ARLACEL 186 (available from ICI Americas Inc.) which includes, in addition to glycerol monooleate, propylene glycol (10%). The main fatty acids of MYVEROL 18-99 are oleic acid (61%), linoleic acid (21%), linolenic acid (9%) and palmitic acid (4%). Suitably in such long-chain monoglycerides, the major fatty acid component is a C_{18}-saturated, monounsaturated or polyunsaturated fatty acid, preferably a C_{18}-monounsaturated or polyunsaturated fatty acid. Suitably the monoglyceride will have an HLB value in the range of about 2.5 to 6. The HLB value of the product MYVEROL 18-99 is 3.7.

In the present invention the amphiphilic substance is preferably glyceryl mono-oleate (mono-olein). As indicated above, in its commercially available form, glyceryl mono-oleate is a material which is predominantly glyceryl mono-oleate but also contains minor amounts of related mono and di-glycerides. Accordingly, the amount that is effective in a particular spray formulation will vary dependent on the level of glyceryl mono-oleate in the commercial material used.

To obtain a sprayable formulation, the amphiphilic substance is combined with a liquid diluent. The diluent is selected on the basis of compatibility e.g. producing a stable blend with the amphiphilic agent, and the ability to achieve a sprayable blend without excessive dilution that will reduce the self-association on contact with water and detract from the desired viscosity increase. Typically, a diluent is a pharmaceutically acceptable oil, most preferably a fatty acid triglyceride, typically vegetable (i.e. plant derived) oil, since mineral oils such as paraffin oil have been implicated in undesirable side effects when inhaled. Suitable vegetable oils include coconut oil, sesame oil and soya bean oil. In this invention, the preferred diluent is a vegetable oil, most preferably coconut oil, that has been fractionated so that it is predominantly medium chain length triglycerides. Typically the proportion of amphiphilic agent to oil is from 2:1 to 1:4, preferably 1:1 to 1:2. Ideally, the amount of diluent is adjusted so that the formulation is of a viscosity that is suitable for spray delivery at 20°C or above.

Suitable medium-chain fatty acid triglycerides for use in the present invention may be of natural, semi-synthetic or synthetic origin and may include blends of different medium chain fatty acid triglycerides. The term "medium-chain fatty acid" as used herein refers to a fatty acid having from 6 to 12, preferably 8 to 10 carbon atoms which may be branched

or unbranched, preferably unbranched and which may be optionally substituted. Certain neutral plant oils, such as fractionated coconut oils, provide convenient sources of medium-chain fatty acid triglycerides. The triglyceride suitably comprises from 50 to 100% (w/w) of caprylic (C_8) acid and from 0 to 50% (w/w) of capric (C_{10}) acid triglycerides. Suitable examples include those available under the trade names MYRITOL; CAPTEX (Karlshams Lipid Specialties, Columbus OH), for instance CAPTEX 355, CAPTEX 300, CAPTEX 350, CAPTEX 850 and CAPTEX 8000; MIGLYOL (BASF), for instance the grades MIGLYOL 810, MIGLYOL 812 AND MIGLYOL 818 (which also comprises a linoleic acid triglyceride) and MAZOL 1400 (Mazer Chemical, Guernee, II). The fatty acid content of representative products is: CAPTEX 355™ - CAPROIC ACID (2%), CAPRYLIC ACID (55%) and capric acid (42%); CAPTEX 8000 - at least 98% caprylic acid, MYGOL 810 - caproic acid (2%), caprylic acid (65-75%), capric acid (25-35%) and MIGLYOL 812 - caproic acid (3%), caprylic acid (50-65%), capric acid (30-45%) and lauric acid (5%) (manufacturer's data).

The sprayable formulations of this invention are especially suitable for nasal delivery, because in the humid environment of the nasal passages they increase in viscosity by contact with water, and so are better able to resist wash-out when in contact with nasal surfaces. The prolonged residence time of formulations of the present invention in the nasal passages, especially the nasal pharynx, makes them particularly suitbable for topical treatment with local action or, since it provides prolonged contact of the formulation with an absorptive region, systemic delivery of a medicament.

Suitable medicaments include antibiotics, for instance mupirocin or a pharmaceutically acceptable salt or ester thereof

An antibiotic such as mupirocin may be used in the prophylactic treatment of recurrent sinusitis, and otitis media.

Suitable pharmaceutically acceptable salts of mupirocin are well known in the art and include alkali metal salts such as sodium and lithium and alkaline earth metal salts such as calcium, of which the calcium salt is preferred, in particular the crystalline dihydrate from thereof described in EP 0 167 856-A (Beecham Group). Other suitable salts include silver and aluminium salts and ammonium and substituted- ammonium salts. The salts may be anhydrous or may be in the form of pharmaceutically acceptable solvates, for instance alcoholates and, especially, hydrates. Preferred salts include the calcium, silver and lithium salts, in particular the calcium salt. In the case of the calcium salt of

mupirocin, the crystalline salt is preferably used, especially the crystalline hydrated calcium salt, more preferably the crystalline dihydrate salt.

Suitable pharmaceutically acceptable esters of mupirocin are well known in the art and include lower alkyl esters, especially the methyl and ethyl esters.

Since the medicament is suspended in a non-aqueous carrier, it is preferably present as a finely divided powder. This may be achieved by milling, and most suitably by micronising (fluid energy milling) so that the medicament has a particle size less than 100 μm, preferably less than 10 μm.

Typically an antibiotic will be used at between 0.1 and 10%, preferably 2 and 8%, typically about 4-6%, by weight of the formulation. It is preferred to use a relatively high dosage level, to reduce the risk of the development of bacterial resistance. Also, to avoid excessive spray volumes which will be uncomfortable in nasal administration, the medicament is preferably present at a relatively high loading compared to other topical administration formulations. For example, mupirocin may be added at a level of 4% w/w to a carrier based on coconut oil and glycerylmono-oleate, so that a sprayed dose of 125 μl will deliver approximately 5 mg approximately 5 mg of mupirocin.

Formulations of the present invention may be administered by a conventional pump dispenser suitable for nasal administration. For treatment of recurrent sinusitis and otitis media the formulation is preferably sprayed into the nasal passages where natural processes carry the medicament through the nasal passages to reach deep seated sites of infection. The viscosity increase on contact with moisture prolongs the residence of the medicament and prevents early wash-out.

In the use and method of this invention, the amphiphilic agent and non-aqueous diluent are typically in the preferred forms described above.

The composition of this invention may be produced by conventional pharmaceutical techniques. Thus, for example, amphiphilic substance and diluent may be blended by mixing together at an elevated temperature. The mixture may then be cooled to room temperature, and, after the addition of any further optional ingredients, stirred to ensure adequate dispersion. The medicament may be added during hot preparation of the base, or may be added with additional ingredients after cooling of the base. If necessary, the composition may be provided in sterile condition.

Optional ingredients that may be added if desired include colourings and flavourings.

Surprisingly it has been found that the addition of the calcium salt of Mupirocin to a mixture of glyceryl mono-oleate and fractionated coconut oil improves the physical stability and rheology of the resulting blend.

The invention is illustrated by the following Example.

Example

A carrier for a nasal spray formulation was prepared by forming a blend of 67% w/w fractionated coconut oil (medium chain length)* and 33% w/w of glyceryl mono-oleate **. To this blend was added 0.2% w/w of powdered lemon juice flavour, followed by 4% w/w of micronized calcium Mupirocin.

The resultant formulation has a viscosity which is sprayable at 20°C or above. When sprayed into the nose of a patient, the liquid coats the nasal passages and contact with moisture inside the nose (from the mucous membranes, and the humid environment generally) causes the carrier to thicken. This prolongs the residence time of the sprayed formulation on the nasal surfaces. A spray volume of about 125 µl contains approximately 5 mg Mupirocin.

*Commercial product Miglyol, obtainable from Hüls

** Commercial product Myverol 18-99, obtainable from Eastman

CLAIMS

1. A sprayable composition adapted for prolonged residence in the nasal passage, in particular the nasal pharynx, which comprises:
(a) an amphiphilic agent that increases in viscosity on contact with water;
(b) a non-aqueous diluent for the amphiphilic agent,
(c) a powdered medicament in suspension.

2. A composition according to claim 1, in which the amphiphilic agent is selected from mono-glycerides, phospholipids and galactolipids.

3. A composition according to claim 2, in which the amphiphilic agent is glyceryl mono-oleate (mono-olein).

4. A composition according to any one of claims 1 to 3, in which the diluent is a pharmaceutically acceptable oil.

5. A composition according to claim 4, in which the diluent is a fatty acid triglyceride oil.

6. A composition according to claim 5, in which the fatty acid triglyceride oil is coconut oil, sesame oil or soya bean oil.

7. A composition according to claim 5 or 6, in which the fatty acid triglyceride has been fractionated so that it is predominantly medium chain length triglycerides.

8. A composition according to any one of claims 4 to 7 in which the proportion of amphiphilic agent to oil is from 2:1 to 1:4.

9. A composition according to any one of claims 1 to 8, in which the medicament is an antibiotic.

10. A composition according to claim 9, in which the antibiotic is mupirocin, or a pharmaceutically acceptable salt or ester there of.

INTERNATIONAL SEARCH REPORT

Int tional Application No
PCT/EP 98/04972

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/00 A61K47/00 A61K31/35

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 98 14189 A (SMITHKLINE BEECHAM O.) 9 April 1998 see the whole document -/--	1-10

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Name and mailing address of the ISA	Authorized officer
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 13528 A (DUMEX-ALPHARMA A/S) 17 April 1997 see page 1, line 3 - line 7 see page 1, line 16 - page 3, line 8 see page 3, line 11 - page 4, line 2 see page 4, line 3 - line 7 see page 4, line 24 - page 5, line 5 see page 8, line 29 - page 11, line 15 see page 12, line 11 - page 13, line 7 see page 17, line 15 see page 18, line 1 see page 20, line 17 - page 21, line 8 see page 21, line 12 - line 19 see page 21, line 28 - page 22, line 4 see page 22, line 25 - line 26 see page 23, line 1 - line 8 see page 25, line 9 see page 26, line 3 see page 26, line 13 - line 15 see page 27, line 5 - line 11 see page 47, line 10 see examples 6,7,9 see page 58, line 1 - page 59, line 19 see page 59, line 30 - line 33 see page 65, line 5 - line 8 see claims 1-4,24-41,71-74,82-84,88	1-10
X	US 4 790 989 A (BEECHAM GROUP PLC) 13 December 1988 see column 4, line 67 - column 5, line 42 see column 6, line 5 - line 12 see column 6, line 66 - column 7, line 12	1-10

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 98/04972

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9814189 A	09-04-1998	AU 4562397 A	24-04-1998
WO 9713528 A	17-04-1997	AU 7279296 A	30-04-1997
		CA 2231273 A	17-04-1997
		EP 0871489 A	21-10-1998
		NO 981633 A	04-06-1998
US 4790989 A	13-12-1988	AU 600264 B	09-08-1990
		AU 7132987 A	07-01-1988
		DE 3780091 A	06-08-1992
		DK 186087 A	27-12-1987
		EP 0251434 A	07-01-1988
		GR 3005660 T	07-06-1993
		IE 59628 B	09-03-1994
		JP 63008331 A	14-01-1988